Evolutionary genetics: **The economics of mutation**

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The presence of mutator genotypes in populations of bacteria may be favoured by selection because they produce rare beneficial mutations and thereby increase the rate of adaptive evolution. Recent work, however, shows that the relationship between mutation rates and adaptive evolution is more complicated.

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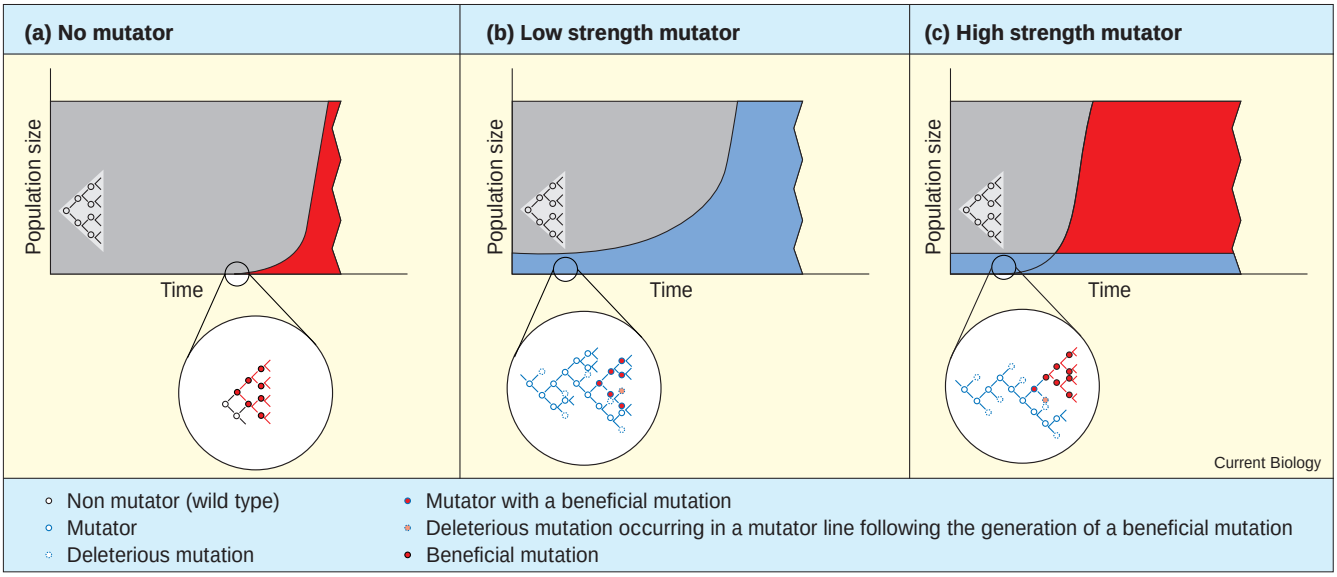
In a capitalist economy the long-term pace of economic growth is to a large measure a function of the rate of technological innovation, but the relationship is rarely ever straightforward. In the short term, a sudden burst of innovation is as likely to fuel economic growth as it is to slow it down, and predicting the causes and effects of fluctuations in factors such as labour supply, production, consumer demand and currency value is problematic. To some extent the relationship between innovation and economic growth parallels the relationship that biologists believe exists between mutation rate and the pace of adaptive evolution. Biologists used to feel they understood the basic causal connections underlying this relationship, but recent results indicate matters are more complex than they thought.

From the elaborate enzymatic machinery involved in DNA replication and repair [1], it is clear that mutation rate is under genetic control and is therefore subject to selection. Given that most mutations are deleterious, selection is likely to operate to minimise mutation rate by favouring mutations in genes that increase the fidelity of DNA replication and repair. However, evolution is ultimately dependent on the production of beneficial mutations and therefore the mutation rate cannot be too low, or species will be unable to adapt to environmental change [2]. This has led to the general view that the rate of adaptive evolution is determined primarily by selection and will be greatest in novel or fluctuating environments, because alterations in mutation rate that increase variation will be favoured under these conditions [2–5].

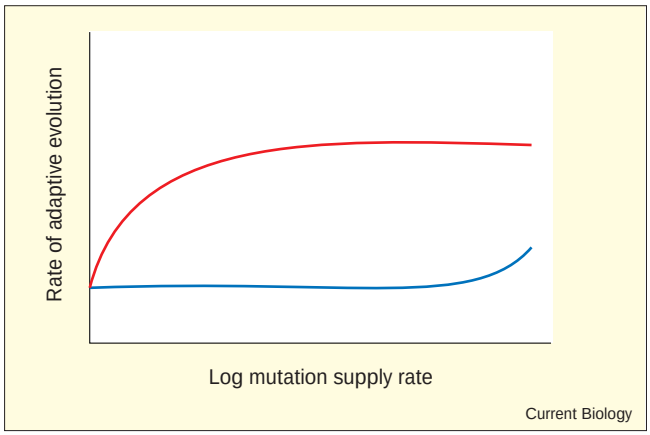
Experimental evidence that an elevated mutation rate can be adaptive was obtained nearly thirty years ago by Cox

Figure 1



Theoretical analysis of the role of mutator alleles in adaptive evolution [12]. (a) A population without a mutator genotype requires a greater length of time before the first adaptive mutation arises and sweeps through the population. (b) A low strength mutator – conferring a10-fold increase in mutation rate over wild type – can 'hitchhike' to fixation as a result of a beneficial mutation arising within the mutator population. (c) A high strength mutator – conferring a 1,000-fold increase in mutation rate over wild type – is unable to hitchhike to fixation; nevertheless, the mutator greatly increases the probability of beneficial mutations and can still increase the pace of adaptive evolution. This effect is explained by the high reversion rate which eliminates linkage with favourable mutants.

Figure 2



Effect of mutation supply rate on rate of adaptive evolution in asexual populations of *E. coli* [14]. The red curve shows an initially poorly adapted population, where the rate of adaptive evolution is initially limited by the mutation supply rate; as the supply rate increases, however, clonal interference becomes an important factor and the rate of adaptive evolution soon reaches an upper 'speed limit'. In an initially well-adapted population, the chance of a beneficial mutation arising is low and so clonal interference is less important. The blue line shows that the well-adapted population experiences a proportional acceleration of adaptive evolution only at the extreme range of mutation supply rates.

and colleagues [6], who competed 'mutator' strains of *Escherichia coli* — strains containing defects in a gene, *mutT*, involved in DNA repair — against wild-type strains in chemostats. Competing mutator strains were found to have a fitness advantage over wild-type strains, which stemmed from the fact that the mutator generated more beneficial mutations [7]. Consistent with expectations, the advantage of the mutator strain was shown to be frequency dependent, so that below a threshold level — ~1/10,000 of the population — the mutator went extinct, because the probability of a beneficial mutation arising in the wild-type population was greater than in the much smaller mutator population. Above this level, however, the mutator always increased in frequency, because beneficial mutations had a greater chance of arising in the mutator strain and their selective advantage caused the linked mutator to hitchhike to high frequency.

After these early results were published, experimental research into the population effects of mutators waned rather, possibly because their evolutionary significance was considered minimal on account of their inability to increase in frequency in a population from a very low level. Then, in 1996, came the first of several reports that described the occurrence of high frequencies (1–5%) of mutators in natural populations of pathogenic [8] and commensal organisms [9]. Moreover, mutators were discovered in three out of twelve *E. coli* populations subject to long-term laboratory selection [10], showing that mutators can arise spontaneously and hitchhike to high frequencies. Additional interest was sparked because of the discovery that defects in the methyl-directed mismatch repair enzymes — a common cause of the mutator genotype in bacteria — also occur in humans and lead to the development of certain types of cancer [11].

The discovery of a high frequency of naturally occurring mutator strains in bacteria prompted further theoretical work to examine the likely impact of elevated mutation rates on the evolution of bacterial populations [12]. The results of simulations assuming infinite population size in changing or novel environments confirmed that mutator genes in asexual populations accelerate the pace of adaptive evolution (Figure 1). Furthermore, they predicted that the rate of adaptation could be enhanced by a strong mutator allele that itself was maintained at a low frequency in the population (Figure 1c). That such a strong mutator allele could continue to have a beneficial effect and yet remain rare was explained by the increased probability of the mutator allele reverting to the wild-type state and thus destroying linkage between the mutator and the beneficial mutation.

Taken at face value, the model of Taddei *et al.* [12] predicts a causal relationship between mutation supply rate and the rate of adaptive evolution, but is an increase in the rate of adaptation the inevitable consequence of an increase of the mutation rate? Taddei *et al.* themselves cast some doubt on this in their own modelling of finite *E. coli* populations, and caution was urged by the inconclusive correlation between mutability and fitness found among the long-term *E. coli* lines [11]. Further reason to pause and reconsider was provided by two recent papers, one theoretical [13] and the other experimental [14].

In the first of these papers, Gerrish and Lenski [13] developed population genetic models which predict that the rate of adaptive evolution will increase proportionately with mutation rate in asexual organisms *only* if populations spend most of their time waiting for beneficial mutations. The logic of this is elegant and simple; if more than a single beneficial mutation is present among different lineages within a population then competition will limit their spread [15], a phenomenon referred to as clonal interference. Clonal interference is likely to be most pronounced in large, poorly-adapted populations with high mutation rates, whereas small, well-adapted populations with low mutation rates should be little affected. Of course in the latter there may be no adaptive evolution, but in the former, the previously presumed benefits of an elevated mutation supply rate are no longer so certain.

In fact, the question becomes not whether elevated mutation supply rates affect the rate of adaptive evolution, but under what conditions are mutator genotypes important for microbial evolution? To determine this,

de Visser *et al.* [14] examined the effect of mutation rate, population size and level of adaptedness on the rate of adaptive evolution of *E. coli*. They found that the rate of adaptive evolution was proportional to the mutation supply rate only under the specific circumstances of small or initially well-adapted populations, where clonal interference was minimal. In other populations, where the mutation supply rate was considerably greater, the rate of adaptive evolution was not proportionally accelerated, and in fact the returns from additional increments in mutation supply were inversely related to their effects. From this arose a further surprising discovery: that the rate of adaptive evolution in asexual populations has an upper 'speed limit' that is independent of the supply of variation (Figure 2).

In the complex spheres of biological systems and human activities, simple cause and effect relationships rarely ever hold. In economics, predicting the short-term effects of the myriad factors that impact on economic growth is problematic, and unravelling the underlying causes can be a demanding if not at times impossible task. It appears that the relationship between the causes and effects of the evolutionary forces that together affect the rate of adaptive evolution is equally uncertain. Elevated mutation rates in asexual populations are not necessarily the result of selection optimising the rate of adaptive evolution in the face of a changing environment. Mutators can increase to high frequency simply by hitchhiking with beneficial mutations to which they are linked; moreover, mutators need not – and often will not – substantially accelerate adaptive evolution [14].

Finally, much has been made of the importance of mutators in the evolution of bacteria in the natural environment, for example, in pathogenesis and antibiotic resistance [10,12,16]. Does knowledge of the diminishing returns of increased mutation supply rate mean that mutators will become a side issue? I doubt it. de Visser *et al.* [14] point out that bacterial pathogens frequently pass through bottlenecks as they transfer from one host to the next, and it is under these conditions that mutators will have the greatest impact on adaptation, and clonal interference the least. In extrapolating to the natural environment, there are least two additional factors to consider: the frequency of recombination and environmental heterogeneity. Sex allows beneficial mutations to be combined into the same lineage [15], while the complex array of ecological opportunities presented in most natural habitats causes lineages to diverge [17]. Both factors will act to reduce the impact of clonal interference.

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References

1. Friedberg EC, Walker GC, Siede W: *DNA Repair and Mutagenesis.* Washington DC: ASM Press; 1995.
2. Kimura M: On the evolutionary adjustment of spontaneous mutation rates. *Genet Res* 1967, 9:23-34.
3. Sturtevant AH: Essays on evolution. I. On the effects of selection on the mutation rate. *Q Rev Biol* 1937, 12:464-476.
4. Drake JW, Charlesworth B, Charlesworth D, Crow JF: Rates of spontaneous mutation. *Genetics* 1998, 148:1667-1686.
5. Leigh EG: The evolution of mutation rates. *Genetics* 1973, 73 (suppl):1-18.
6. Gibson TC, Scheppe ML, Cox EC: Fitness of an ***Escherichia coli*** mutator gene. *Science* 1970, 169:686-688.
7. Chao L, Cox EC: Competition between high and low mutating strains of ***Escherichia coli***. *Evolution* 1983, 37:125-134.
8. LeClerc JE, Li B, Payne WL, Cebula T: High mutation frequencies among ***Escherichia coli*** and ***Salmonella*** pathogens. *Science* 1996, 274:1208-1211.
9. Matic I, Radman M, Taddei F, Picard B, Doit C, Bingen E, Denamur E, Elion J: Highly variable mutation rates in commensal and pathogenic ***Escherichia coli***. *Science* 1997, 277:1833-1834.
10. Sniegowski PD, Gerrish PJ, Lenski RE: Evolution of high mutation rates in experimental populations of ***E. coli***. *Nature* 1997, 387:703-705.
11. Modrich P: Mismatch repair, genetic stability and tumour avoidance. *Phil Trans Roy Soc Lond [Biol]* 1995, 347:89-95.
12. Taddei F, Radman M, Maynard Smith J, Toupance B, Gouyon PH, Godelle B: Role of mutator alleles in adaptive evolution. *Nature* 1997, 387:700-702.
13. Gerrish PJ, Lenski RE: The fate of competing beneficial mutations in an asexual population. *Genetica* 1998, 102/103:127-144.
14. de Visser JAGM, Zeyl CW, Gerrish PJ, Blanchard JL, Lenski RE: Diminishing returns from mutation supply rate in asexual populations. *Science* 1999, 283:404-406.
15. Muller JH: The relation of recombination to mutational advance. *Mutat Res* 1964, 1:2-9.
16. Moxon ER, Thaler DS: The tinker's evolving tool-box. *Nature* 1997, 387:659-662.
17. Rainey PB, Travisano M: Adaptive radiation in a heterogeneous environment. *Nature* 1998, 394:69-72.